IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 94247; 58898/130

In re patent application of
David J. BOVA
Serial No.: 08/368,378
Filed: June 14, 1995
Group Art Unit: 1502
Examiner: J. Venkat

For: NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREOF

DECLARATION UNDER 37 CFR §1.131

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, David J. Bova, state and declare that:

1. I am the named inventor of the above-captioned application, which is a continuation-in-part application of U.S. serial No. 08/124,392, filed on September 20, 1993 ("the parent application").

2. In the office action of November 27, 1995, the examiner maintained a rejection of claims 1-9 under 35 USC §102(e), as being anticipated by O'Neill *et al.*, U.S. patent No. 5,268,181 (1993), which was filed on June 29, 1992.

3. As Vice President of Research and Development for KOS Pharmaceuticals, Inc., I prepared a protocol to compare the effect on serum lipids of sustained release nicotinic acid that was administered once-a-day (either in the evening or at night) or twice-a-day during the day. KOS Pharmaceuticals, Inc., the assignee of the above-captioned application, sponsored the study, and I monitored the performance and conduct of the study.

4. The KOS Pharmaceuticals study was conducted with male and female patients having total cholesterol levels greater than

Exhibit A

250 mg/dl. The selection criterion for patients was based upon the report of an expert panel of the National Cholesterol Education Program, which was published in *Arch. Intern. Med. 148*: 36 (1988). A copy of the report is attached to this declaration as Exhibit 1. The panel concluded that individuals with blood cholesterol levels ≥ 240 mg/dl should be classified as having "high" cholesterol levels. Therefore, the patients included in the KOS Pharmaceuticals study were considered to have high cholesterol levels, and they were classified as hyperlipidemics. Accordingly, the study was performed to determine a method of treating hyperlipidemia in hyperlipidemics comprising the administration of an effective amount of nicotinic acid once per day in the evening or at night, as stated in claim 1. Relevant sections of the study protocol were attached as Exhibit A in my declaration of August 17, 1995.

5. The results of the KOS Pharmaceuticals study were disclosed in the above-captioned application and in the parent application. The relevant pages of the parent application are attached to this declaration as Exhibit 2. Briefly, we found that the mean blood cholesterol level at baseline and prior to treatment was 282.2 mg/dl. In the group that received nicotinic acid once per day at night, the mean blood cholesterol level decreased 12.3% to 246.9 mg/dl. Analysis of the clinical data revealed that this decrease in blood cholesterol was highly statistically significant. Thus, the administration of a sustained release formulation of nicotinic acid (once per day in the evening or at night) is an effective treatment for hyperlipidemia.

6. The KOS Pharmaceuticals study began in 1990, and the study was conducted in the United States. Data analyses were also performed in the United States. Although the last visit for the last patient took place on March 20, 1991, statistical analyses were performed each time data was entered into the database.

Exhibit 3 presents an analysis of data that had been collected by December 31, 1990, and demonstrates that a statistically significant reduction in total cholesterol was observed by that time. Exhibit 3 also includes copies of medical documents containing the clinical data used in the analysis.

7. As described above, the KOS Pharmaceuticals study verified a method of treating hyperlipidemia in a hyperlipidemic comprising the administration of nicotinic acid once per day in the evening or at night. Moreover, nicotinic acid was administered to patients in combination with a pharmaceutically acceptable carrier. Accordingly, the invention presently described in claim 1 was conceived and reduced to practice in the United States prior to June 29, 1992, the filing date of the O'Neill patent.

8. In the KOS Pharmaceuticals study, patients received nicotinic acid in the form of sustained release tablets containing nicotinic acid, hydroxypropylmethylcellulose, Povidone and stearic acid, as shown in Table I of both the above-captioned application and the parent application. See page 6 of the parent application, which is attached to this declaration as Exhibit 4. Povidone is also known as "polyvinylpyrrolidone," as stated in monograph 7700 in THE MERCK INDEX, 11th Edition (Merck & Co. 1989) at page 1219. See Exhibit 5. We included stearic acid in the formulation of the study as a lubricating agent. See, for example, the parent application at page 5, fourth full paragraph. Accordingly, the use of a formulation for treating hyperlipidemia that comprises nicotinic acid, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the lubricant, stearic acid, antedates the filing date of the O'Neill patent.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false

Serial No. 08/368,378

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 3/27/96 By: David J. Bova

David J. Bova

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of

DAVID J. BOVA

Serial No. 08/368,378

Filed January 14, 1995

For NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREFOR

Group Art Unit 1205

J. Venkat, Examiner

I hereby certify that this correspondence was deposited with the United States Postal Service as first class mail in an envelope addressed to: Box NON-FEE AMENDMENT Assistant Commissioner for Patents, Washington, D.C. 20231 on this 23rd day of August, 1995

Norma J. Nazarewicz, Sec'y to Douglas J. Hura

DECLARATION UNDER 37 CFR §1.131 OF PRIOR INVENTION IN THE UNITED STATES TO OVERCOME CITED PATENT

ASSISTANT COMMISSIONER FOR PATENTS

Washington, D.C. 20231

Sir:

The undersigned declares as follows:

1. He is the sole named inventor in U.S. Patent Application Serial No. 08/368,378.

2. The purpose of this Declaration is to show that the present invention was made in the United States prior to June 29, 1992, which is the filing date of U.S. Patent No. 5,268,181.

3. As evidence that the present invention was made in the United States prior to June 29, 1992, there is attached hereto as Exhibit A, relevant portions of a document entitled "A SINGLE BLIND PLACEBO CONTROLLED PILOT STUDY COMPARING THE EFFECT OF ONCE-A-DAY VERSUS TWICE-A-DAY DOSING OF SUSTAINED RELEASE NIACIN ON SERUM LIPIDS".

Exhibit B

4. The date of Exhibit A is prior to June 29, 1992, and Actual dates and other non-relevant information has been masked from Exhibit A.

5. Exhibit A was prepared in the normal course of my employment with the Assignee of record. The experiments described therein, and hence, the reduction to practice of the present invention, were made in the United States prior to June 29, 1992.

Further Declarant sayeth not.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

8/17/95
Date

David J. Bova
David J. Bova

COPY

A SINGLE-BLIND PLACEBO CONTROLLED PILOT STUDY COMPARING THE EFFECT OF ONCE-A-DAY VERSUS TWICE-A-DAY DOSING OF SUSTAINED RELEASE NIACIN ON SERUM LIPIDS

PROTOCOL NUMBER:

EXHIBIT
A

1. BACKGROUND

Niacin has been known to reduce serum cholesterol for many years. In large doses of 1000 mgs given three times a day with meals, studies indicate the reduction is 10-25%. Immediate release niacin is currently approved by the US Food and Drug Administration (FDA) for this indication. Immediate release niacin has not received widespread acceptance, however, because of its poor side effect profile and lack of patient compliance. Sustained release dosage forms of niacin have been developed and tested in the past as a means of reducing the side effects which are typical of niacin therapy. To date none have received FDA approval for this indication.

2. PURPOSE OF STUDY

The purpose of this study is to compare the effect of two different dosing schedules of sustained release niacin on serum lipids and to evaluate the use of aspirin to alleviate the flushing typically encountered as a side effect when initiating niacin therapy.

3. DESIGN

This study is a single-blind placebo-controlled pilot study comparing 4 tablets of 375 mgs sustained release niacin dosed once-a-day at night and 2 tablets of 375 mg of sustained release niacin dosed twice-a-day, two tablets after breakfast and 2 tablets before bedtime for a total daily dose of 1500 mgs. A 1 week lead-in period to establish baseline serum lipid levels has been incorporated into the study protocol. At the end of this lead-in period, a test dose of 1500 mg of sustained release niacin will be administered. Patients will be randomized into three study groups. Two groups will receive active treatment (group A or B) and one group will receive placebo treatment (group C).

Patients who complain of flushing after receiving the test dose will receive a combination of sustained release niacin and enteric coated aspirin, intended to reduce the incidence of flushing, for the first four (4) weeks of the treatment period in the active treatment group (group A or B). These patients will then be switched to plain sustained release niacin for the last four (4) weeks of treatment. Patients who do not complain of flushing will continue to receive sustained release niacin during the entire eight (8) week treatment period in the active treatment group (group A or B). A control group of patients will recieve 4 placebo tablets once-a-day for the entire eight (8) week treatment period (group C). Patients will be blinded as to the type of treatment they receive, active or placebo.

4. NUMBER OF PATIENTS/PATIENT GROUPS

GROUP A: 12 patients will be dosed once-a-day with active treatment
GROUP B: 12 patients will be dosed twice-a-day with active treatment
GROUP C: 6 patients will be dosed once-a-day with placebo

A total of 30 subjects, 1 center will complete this study

PROTOCOL NUMBER:

TITLE: A Single-Blind Placebo-Controlled Pilot Study Comparing the Effect of Once-a-Day versus Twice-a-Day Dosing of Sustained Release Niacin on Serum Lipids

PRINCIPAL INVESTIGATOR:

Craig Price, M.D.
Pharm Evaluations Services, Inc.
A Division of Health & Sciences Research, Inc.
16244 S. Military Trail
Suite 590
Delray Beach, FL 33484
Phone: (407) 496-0221

Craig C. Price M.D.
(Signature) (Date)

CONTACT FOR KOS PHARMACEUTICALS, INC.:

Suzanne Balandis, R.Ph.
KOS Pharmaceuticals, Inc.
801 Brickell Avenue
Suite 1006
Miami, FL 33131
Phone: (305) 577-3466

Suzanne Balandis
(Signature) (Date)

SPONSOR:

KOS Pharmaceuticals, Inc.
801 Brickell Avenue Suite 1006
Miami, FL 33131
Phone: (305) 577-3466

ANTICIPATED START DATE:

ANTICIPATED COMPLETION DATE:

TOTAL NUMBER OF PATIENTS: 30 patients

DESCRIPTION OF MEDICATIONS:

Generic Name	Dosage Form	Maximum Daily Dose	Classification
Niacin	oral	1500 mgs Niacin	vitamin
Niacin/aspirin	oral	1500 mgs Niacin 324 mgs Aspirin	vitamin analgesic
Placebo tablets	oral	----	----

ADDRESS OF INSTITUTIONAL REVIEW BOARD:

5. INDICATION

Reduction of serum cholesterol

6. DURATION OF TRIAL

Approximately 10 weeks for each patient

7. CONSENT STATEMENT

A written informed consent in accordance with established criteria of an approved Institutional Review Board and appropriate sections of the Federal Register must be signed by each patient. The original signed consent form must be filed with the investigators' copies of the Case Report for each subject. A blank copy of the consent form is attached to this protocol (see Appendix 1).

8. INSTITUTIONAL REVIEW BOARD APPROVAL

Institutional Review Board approval is required prior to commencing this study. A copy of the Institutional Review Board's approval of the protocol must be forwarded to KOS by the investigators.

9. ACCOUNTABILITY OF STUDY MEDICATION

Inventory ledgers will be issued to the investigator with the medication, and all medication received by the investigator will be inventoried. A log of the dispensing of medication to each patient will be maintained on this inventory ledger. All medication containers and unused medication must be returned to KOS for accountability.

10. PATIENT SELECTION CRITERIA

A. Males or females over the age of 40 years old

B. Individuals whose baseline serum cholesterol levels are equal to or greater than 260 mg/dL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 94247; 58898/130

In re patent application of
David J. BOVA
Serial No.: 08/368,378
Filed: June 14, 1995
Group Art Unit: 1502
Examiner: J. Venkat

For: NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREOF

DECLARATION UNDER 37 CFR §1.132 OF DR. ARTHUR RAINES

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Arthur Raines, Ph.D., state and declare that:

1. I am a Professor of Pharmacology at Georgetown University in Washington, D.C. My Curriculum Vitae is appended hereto as Exhibit 1.

2. I understand that the examiner of the above-captioned application has maintained a rejection of the claims under 35 USC §102(e), as being anticipated by O'Neill *et al.*, U.S. patent No. 5,268,181 (1993) ("the O'Neill patent"). I also understand that the basis of the rejection is that the O'Neill patent discloses a method of treating hyperlipidemia comprising the administration of a single daily dose of a particular niacin composition, preferably, at, or immediately following, the evening meal, but before bedtime. I further understand that the examiner has taken the position that the administration of niacin in the evening or at night is supported by the parent application of the O'Neill patent (Evanstad *et al.*, U.S. patent No. 5,126,145 (1992)["the Evanstad patent"]), which teaches the administration of niacin twice daily. In particular, the Evanstad patent states that "[t]ablets can be scored to permit dasy [*sic*] breakage into smaller doses for titration up to the standard 750 mg. dose given twice daily." Evanstad patent at column 5, lines 58-60.

Exhibit C

3. My review of the Evanstad patent revealed that the patent discloses a formulation of a sustained release tablet suitable for use with highly water soluble drugs, which can present formulation problems. The Evanstad patent describes the use of hydroxypropyl methylcellulose and other ingredients to retard the dissolution of water soluble drugs and thus prolong the period of their absorption. Accordingly, the patent is entitled "Controlled release tablet containing water soluble medicament."

4. The Evanstad patent indicates that niacin, which is the water soluble agent used as an example of the invention, could be administered twice a day. See the Evanstad patent at column 5, lines 54-62. According to the patent, the stated purpose of the sustained release is to aid in avoiding side effects (which might occur with a standard tablet dosage form where release usually occurs more rapidly and can lead to headache, dizziness, tingling and flushing). At no point in the patent is the issue of a specified time of administration of niacin mentioned, nor is the issue of diurnal variation in lipid biosynthesis addressed; therefore, the timing of the dose to a particularly appropriate part of the day to enhance efficacy is not a component of the Evanstad patent.

5. On the other hand, my review of the O'Neill patent revealed that the document specifically addresses the issue of administering the niacin at a specified time period based on the variation in lipid biosynthesis which occurs over the 24 hour time period. See the O'Neill patent at column 2 (lines 45-53), column 3 (lines 15-22) and column 10 (lines 34-37). The O'Neill patent calls for the taking of the sustained release dosage form at some time with or after the evening meal or at bedtime. This will presumably allow for medication levels to be optimal at the time of peak synthesis of serum lipids.

6. In summary, the Evanstad patent does not teach or even suggest the O'Neill method of administering niacin at a time of day targeted to coincide with the time at which cholesterol is

maximally synthesized in the human liver. The once daily, diurnal variation-related dose of niacin described by O'Neill cannot be said to follow from the two dose, diurnal variation-unrelated regimen of Evanstad.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: May 22, 1996 By: _____

Arthur Raines

CURRICULUM VITAE Rev.10/1/95

ARTHUR RAINES

MAILING ADDRESS: Department of Pharmacology
Georgetown University
Schools of Medicine and Dentistry
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Washington, DC 20007
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HOME ADDRESS: Route 2, Box 264, Lovettsville, VA 22080

BIRTH: May 9, 1936, New York, New York, U.S.A.

EDUCATION:

1953-1957	Fordham University College of Pharmacy, B.S. Pharmacy
1958-1960	Columbia University College of Pharmacy, M.S. Pharmacology
1960-1965	Cornell University Graduate School of Medical Sciences, Ph.D.

HONORS:

1957	Graduated with Honors from Fordham University
1984	Recipient Golden Apple Teaching Award
1956	Recipient Kaiser-Permanente Award for Excellence in Teaching
1989	Nominee, Golden Apple Award--First and Second Year Medical Classes
1992	Recipient Golden Apple Teaching Award
1994	Recipient Golden Apple Teaching Award

FELLOWSHIPS AND APPOINTMENTS:

1958-1969	Teaching Assistant, Columbia University
1960-1965	U.S.P.H.S. Predoctoral Fellow
1965-1967	U.S.P.H.S. Postdoctoral Fellow
1966-1968	Instructor, Pharmacology, Cornell University Medical College
1968-1969	Assistant Professor, Pharmacology, Cornell University Medical College and Cornell University Graduate School of Medical Sciences
1969-1972	Assistant Professor, Pharmacology, Georgetown University, Schools of Medicine and Dentistry
1969-1972	Lecturer, Walter Reed Army Institute for Research
1971	Supervisory Pharmacologist (Consultant), Bureau of Occupational Safety and Health

1972-1978	Associate Professor, Pharmacology, Georgetown University, Medical, Dental and Graduate Schools
1973-1975	Member, Advisory Committee on Neurology, Food and Drug Administration
1977-1980	Member, Faculty Senate, Georgetown University
1972-present	Member (Ad Hoc), Several NIH Study Sections, Site Visits and Technical Merit Reviews
1979-1982	Curriculum Committee, Dental School
1977-1992	Member, Editorial Advisory Board, Journal of Pharmacology and Experimental Therapeutics
1986-present	Reviewer, New England Journal of Medicine
	Guest Reviewer for Journal articles: Biochemical Pharmacology, Epilepsia, Neuropharmacology, Life Sciences, Canadian Journal of Physiology and Pharmacology, Muscle-Nerve, Epilepsy Research
1978-present	Professor of Pharmacology, Georgetown University Medical, Dental and Graduate Schools
1978-present	Hospital Pharmacy Formulary (P & T) Committee (Acting Chair 5/95 - 11/95
1982-1985	Subcommittee for Scientific Merit Evaluation, Human Research Committee (Institutional Review Board)
1982-1988	Committee on Corporate Interface, Patents and Conflict of Interest Chairman - 7/1/85-7/1/88
1971-1979; 1981-1982	Consultant, Food and Drug Administration
1983-1988	Member, Committee on Students
1979-1980	Member, Committee for Evaluation of Anesthesiology Department
1984-1985	Member, Committee for Evaluation of Surgery Department
1979-1982	Course Director, Dental Pharmacology
1983-1986	Course Director, Medical Pharmacology
1983-present	Education Committee, Medical School (Chair pre-clin. course directors 1994--)
1983-1984	Committee on Preclinical Curriculum
1983-1984	Committee on Academic Environment
1984-1986	Task Force for Teaching of Geriatrics in Medicine
1985-1986	Task Force on Instruction Evaluation
1986-1987	Task Force for Preclinical Teacher Evaluation (Chairman)
1984-present	Member, Scientific Advisory Board, Taro Pharmaceuticals Ltd., Haifa, Israel
1984-present	Consultant, United States Pharmacopeial Convention
1987-present	Delegate, United States Pharmacopeial Convention
1984-1986	Member, Search Committee, Neurology Chairperson
1986-present	Consultant, American Medical Association, Data Evaluation Project
1986-1987	Task Force for Curriculum Modification and Inventory, 2nd Year Medical School (Chairman)
1986-1988	Acting Chairman, Department of Pharmacology, Georgetown University Medical, Dental and Graduate Schools
1987-1988	Task Force for Tuition and Class Size
1988; 1995	Task Force LCME evaluation--faculty(1988) Curriculum (1995)
1988	Task Force (Chairman) Medical School Drug Abuse Policy Formulation

1988 Task Force--Selection Kaiser Permanente Award
1988-present Department Committee on Faculty Recruitment
1989-present Department Committee on Adjunct and Secondary Appointments (Chair)
1989-1990 Vice Chairman, Medical Center Committee on Scientific Fraud and Misconduct
1989-1991 Course Director: Fundamentals of Pharmacology
1989-1990 Member, Search Committee--Chair in Emergency Medicine
1989-1990 Member, Committee for the Evaluation of the Department of Physiology
1990-present Professor of Neurology
1990-present University Committee on Scientific Misconduct (1990-94, Chairman)
1991-present Medical Center Committee on Conflict of Interest
1990-1991 Course Director: Neurology & Neurosurgery Resident course in Advanced Concepts in Neuropharmacology
1991-present Course Director: Medical Pharmacology
1991-present Consultant (Pharmacology/Toxicology): Stedman's Medical Dictionary; Williams & Wilkins Publishers
1992-present Member, Library Committee; Georgetown University Medical Center

1993-present Member, Problem Based Learning Planning Committee.

1993-1995 President, Sigma Xi Research Society, Georgetown University Chapter

1995-present Secretary, Sigma Xi Research Society, Georgetown University Chapter

1995-present President, Amer. Assoc. Univ. Prof. Georgetown University Chapter

1995-present Member, Problem Based Learning Evaluation Committee

PROFESSIONAL SOCIETIES; ELECTED TO MEMBERSHIP:

American Society for Pharmacology and Experimental Therapeutics
Rho Chi Society
Sigma Xi
A.A.A.S.
New York Academy of Sciences
Society for Experimental Biology and Medicine
American Epilepsy Society
Society for Neuroscience
Drug Information Association
International Brain Research Organization
American Chemical Society
American Assn. of University Professors
American College of Clinical Pharmacology (Chesapeak Chptr.)

GRANTS AND AWARDS:

3/67-6/69	Factors influencing the capacity of digitalis to induce cardiac rhythm disorders. New York heart Association [$30,000]
1971-1974	Neuropharmacology of the heart. U.S.P.H.S. [$95,000]
1971-1974	Pharmacology of nerve terminals. U.S.P.H.S. [$105,000]
1/70-12/70	Effects of digitalis on spinal cord function. Washington Heart Association. [$7500]
6/2-6/73	Anticonvulsant effects of diphenylbarbituric acid. NINDS. [$5000]
3/74-3/76	Effects of anticonvulsant drugs on cerebellar function. U.S.P.H.S. [$79,300]
4/76-8/80	Effects of anticonvulsant drugs on cerebellar function. Competitive Renewal. U.S.P.H.S. [$96,744]
7/76-6/80	Effects of drugs on motor systems. U.S.P.H.S. [$163,452]
10/82-9/85	Standardized model for spinal cord injury. NINCDS. [$44,000--part of Program Project]
3/83	Anticonvulsant drug development program. International Biological Research Corporation. [indefinite period, $3,300]
3/88-3/91	Influence of sublethal exposure to Soman on neurologic cardiovascular, respiratory and enzymatic function. U.S. Army Research and Development Command. [$424,400] Co-principal Investigator
7/95	Development of novel anticonvulsant and muscle relaxant comounds : with Darryl Abernethy, M.D. Ph.D. Taro Pharmaceuticals $ 12,500 indefinate period.

INVITED PRESENTATIONS, SEMINARS AND SYMPOSIA

DATE	TITLE	HOST AND PLACE
May 1968	The influence of anticonvulsant drugs on motor nerve terminals	Epilepsy Branch, NIH, Salt Lake City, UT
Nov. 1968	The nervous system as a site of action for antiarrhythmic and antiarrhythmogenic drugs	Cardiovascular Research Lab., NIH, Bethesda, MD
Dec. 1968	The influence of diphenylhydantoin on neuromuscular function	Pharmacology Dept., Univ. of Texas Sch. of Med., Galveston, TX
June, 1969	Stabilization of motor nerve endings by diphenylhydantoin	Neurology Dept., Cornel Univ. Sch. of Medicine, New York, NY
March, 1972	The neuropharmacology of anti-epileptic drugs	Pharmacology Dept., Med. Col. of Pennsylvania, Philadelphia, PA
Sept. 1972	Neural control of cardiac function: implications for antiarrhythmic drug actions	Dept. of Pharmacology, Howard Univ. Med. School, Washington, DC
Feb. 1973	Anticonvulsant properties of diphenylbarbituric acid in the mouse	Epilepsy Branch, NIH, Bethesda, MD
Feb. 1976	The influence of phenytoin on sensorimotor function and its relation to treatment in spasticity	Neurology Dept., Cornell Univ. Sch. of Medicine, New York, NY
March, 1976	The use of phenytoin and chlorpromazine in the treatment of spasticity	Neurology Department, Mt. Sinai School of Med., New York, NY
May, 1976	Novel pharmacologic approaches in the treatment of spasticity	Burke Rehabilitation Center, Cornell Med. College, Westchester, NY
May, 1977	Phenytoin Revisited; Symposium Presentation	Pharmacology Dept., Georgetown Univ., Med. Sch., Washington, DC

June, 1977	The influence of phenytoin on experimental hypertonus in the cat; implications for treatment of spasticity	Physiol. & Pharmacol. Dept., Duke Univ. Sch. of Med., Durham, NC
June, 1977	The use of dilantin, with and without thorazine in humans with spasticity	Parke-Davis & Company, Ann Arbor, MI
Dec. 1977	The pharmacologic management of spasticity	Rehabilitation & Physical Therapy Dept., Suburban Hosp., Bethesda, MD
March 1978	The influence of phenytoin on the muscle spindle and its relation to hypertonus in man	Neurology Dept., Cornell Univ. Sch. of Med., New York, NY
Nov. 1978	The actions of phenytoin and chlorpromazine in motor function in cats and humans	Pharmacology Dept., Univ. of West Virginia Sch. of Med., Morgantown, WV
Dec. 1978	Phenytoin's actions on somato-sensory systems	Pharamcology Dept., Cornell Univ. Sch. of Med., New York, NY
Aug. 1979	Effects of anticonvulsants on motor function: implications for mechanisms of action, drug intoxication, anticonvulsant screening procedures and new therapies in spasticity	NIH & ASPET, Portland, OR
Dec. 1979	Pharmacokinetics of anticonvulsant drugs in man with specific reference to toxicity	Neurology Dept., Children's Hosp., Washington, DC
Jan. 1980	Phenytoin as a muscle relaxant in hypertonic disorders	Warner-Lambert Corp., Morris Plains, NJ
June, 1980	New approaches in muscle spasticity	Univ. of Michigan and Warner-Lambert Corp., Ann Arbor, MI
Oct. 1980	Phenytoin action on nerve and muscle	Neurology Dept., Georgetown Univ. Hosp., Washington, DC

May, 1981	The muscle spindle as a target for the actions of phenytoin	Pharmacology Dept., Howard Univ., Washington, DC
Oct. 1981	The effects of phenytoin on sensory and motor systems in the cat	Pharmacology Dept., Univ. of Pennsylvania Col. of Med., Hershey, PA
June, 1984	The effects of phenytoin and chlorpromazine to produce hypotonia in the cat and man	A.H. Robins Pharmaceuticals, Richmond, VA
Aug. 1984	Efficacy of phenytoin and calcium antagonists on organophosphate poisoning	U.S. Army, Chemical & Biological Defense Division, Aberdeen, MD
Oct. 1984	Experimental preclinical and clinical studies on muscle hypertonus of central nervous system origin	Veterans Administration Hosp., Washington, DC
April 1985	Update on the use of newer analgesic agents	Dental Study Group of the Washington Metropolitan Area, Washington, DC
April 1985	Muscle relaxant properties of phenytoin in the cat and man	Dept. of Neurology, Univ. of Indiana Sch. of Med., Indianapolis, IN
April 1985	The role of phenytoin and calcium blockers in organophosphate poisoning	Dept. of Pharmacoogy, Univ of Indiana Sch. of Med., Indianapolis, IN
Feb. 1986	Phenytoin and calcium blockers prevent organophosphate toxicity and enhance protection by atropine and 2-PAM	A.H. Robins Pharmaceuticals, Richmond, VA
May 1986	Pharmacokinetic principles: uptake and distribution of anesthetic drugs and adjuncts to anesthesia	Dept. of Anesthesiology, The Fairfax Hospital, Fairfax, VA
Nov. 1988	Pharmacologic bases for muscle relaxation; relationships to motor systems	Sterling-Winthrop Research Institute, Rensselear, NY

Mar. 1989	Pharmacokinetic factors in determining serum levels of antiepileptic drugs	Dept. of Neurology, Georgetown Univ. Hosp., Washington, DC
May 1989	Pharmacokinetic factors in drug distribution	Dept. of Neonatology, Columbia Hosp. for Women, Washington, DC
June 1990	Protective effects of phenytoin and calcium blockers on organophosphate induced toxicity	Dept. of Pharmacology, Goergetown University Med. Sch., Washington, DC
Mar. 1991	The pharmacology of anxiety	Pharmaceutical Manufacturers Association, Advanced Course
Apr. 1991	Effects of phenytoin and calcium blockers on fasciculations and toxicity produced by anticholinesterase drugs	Dept. of Neurology, Georgetown Univ. Med. Ctr., Washington, DC
Apr. 1995	Anticonvulsant Barbiturates: New Fruit from an Old Tree	Div. Clinical Pharmacology; Georgetown University Med. Ctr.
Nov. 1995	Drug Development of New Anti-convulsant Barbiturates	Dept. of Neurology, Veterans Admin. Hosp. Washington, D.C.

BIBLIOGRAPHY
ARTHUR RAINES

PUBLICATIONS:

Raines, A.: The influence of stress on adrenocortical function in the rat. Masters Dissertation. Columbia University, 1960.

Raines, A.: Effects of diphenylhydantoin on post-tetanic alterations in the terminals of dorsal root fibers and motor nerves. Ph.D. Dissertation. Cornell University, 1965.

Raines, A. and F.G. Standaert: Pre- and post-junctional effects of diphenylhydantoin at the cat soleus neuromuscular junction. J. Pharmacol., 153: 361-366. 1966.

Raines, A. and F.G. Standaert: An effect of diphenylhydantoin on post-tetanic hyperpolarization of intramedullary nerve terminals. J. Pharmacol., 156: 591-597, 1967.

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ABSTRACTS:

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Attorney Docket No. 32892.00002 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this paper, including Attachment 1, are being deposited with the United States Postal Service "Express Mail Post Office to addressee," Express Mail Label No. EE863295453US, under 37 C.F.R. §1.10 on February 26, 1999, and is addressed to the Honorable Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Peter J. Manso, Reg. No. 32,264 — February 26, 1999

February 26, 1999
Express Mail Date
Express Mail Label No. EE863295453US

In re Application of:	David J. Bova
Serial No.:	08/368,378
Filing Date:	January 14, 1995
Group Art Unit:	1931
Examiner:	J. Venkat
Title:	*NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREFOR*

Assistant Commissioner of Patents
Washington, D.C. 20231

February 26, 1999

Dear Sir:

DECLARATION UNDER 37 CFR §1.608(b)

I, George M. Toth, state and declare that:

1. I earned a B.S. in Chemistry at Ursinus College in 1988.

2. I have been employed by Kos Pharmaceuticals, Inc. from about October, 1990 to the present. I am currently the Associate Director of Quality Control at Kos Pharmaceuticals, Inc. A copy of my *curriculum vitae* is submitted herewith as Attachment 1.

3. I was employed by Kos Pharmaceuticals, Inc. during part of the time the study attested to by David Bova in the Declarations was being conducted. In addition, while at Kos

Attachment D

Pharmaceuticals, I was aware of and have personal knowledge of the study referred to in David Bova's two declarations filed as Attachments A and B in the Response After Final (hereinafter "Declarations").

4. I have reviewed copies of the Declarations and, to the best of my knowledge, they are true and accurate.

5. It is my understanding and belief that the Kos Pharmaceuticals' study began on June 11, 1990 and was diligently completed on March 20, 1991, and it was conducted entirely in the United States, as attested to by David Bova in the Declarations. It is my further understanding and belief that Data analyses were also performed in the United States, as attested to by David Bova in the Declarations. It is my further understanding and belief that, although the last visit for the last patient took place on March 20, 1991, statistical analyses were performed each time data was entered into the database, as attested to by David Bova in the Declarations.

6. It is also my understanding and belief that the documents, which accompany the Declarations, represent true and accurate copies of the originals.

7. It is also my understanding and belief that the Kos Pharmaceuticals study attested to by David Bova in the Declarations verified a method of treating hyperlipidemia in a hyperlipidemic comprising the administration of nicotinic acid once per day in the evening or at night, and that the nicotinic acid was administered to patients in combination with a pharmaceutically acceptable carrier. Still further, it is my understanding and belief that the inventions presently described and claimed in claims 1-9 and 15-18 in the above-identified application for U.S. patent were conceived and reduced to practice in the United States prior to June 29, 1992.

8. Still further, it is my understanding and belief that, in the Kos Pharmaceuticals study, patients received nicotinic acid in the form of sustained release tablets containing nicotinic acid, hydroxypropylmethylcellulose, povidone and stearic acid. Still further, it is my

understanding and belief that stearic acid was included in the formulation, which was used in such study, as an external lubricating agent.

9. I have reviewed the copy of the FDA letter, submitted as Attachment E with the Response After Final, and to the best of my knowledge, it is a true and accurate copy of the original.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Titlte 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

02/26/99

Date

George ~~Michael~~ M. Toth
02/26/99

DEPARTMENT OF HE[redacted]H & HUMAN SERVICES [redacted]blic Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-381

JUL 28 1997

KOS Pharmaceutical, Inc.
Attention: Marvin F. Blanford, Pharm. D.
1001 Brickell Bay Drive, Suite 2502
Miami, FL 33131

Dear Dr. Blanford:

Please refer to your new drug application dated May 3, 1996, received May 6, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Niaspan™ (niacin extended-release tablets), 375 mg, 500 mg, 750 mg, and 1000 mg.

We acknowledge receipt of your submissions dated May 22, June 17 and 22, October 29, November 18 and 21, December 10 and 20, 1996, January 14, February 21, April 9, 11, 14, and 29, May 2 and 12, June 10, 12, and 30, and July 2, July 10(3), July 14, July 15(2), and July 16, 1997.

The User Fee goal date for this application is August 6, 1997.

This new drug application provides for use of Niaspan™ for the five following indications: 1) as an adjunct to diet for reduction of elevated total cholesterol, LDL cholesterol, ApoB, and triglyceride levels in adult patients with primary hypercholesterolemia and mixed dyslipidemia (Types IIa and IIb); 2) in combination with a bile-acid binding resin as an adjunct to diet for reduction of elevated total and LDL cholesterol levels in adult patients with primary hypercholesterolemia (Type IIa); 3) as adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them; 4) in patients with history of myocardial infarction and hypercholesterolemia, to reduce the risk of recurrent nonfatal myocardial infarction and; 5) in patients with a history of coronary artery disease (CAD) and hypercholesterolemia, in combination with a bile acid binding resin, to slow progression or promote regression of atherosclerotic disease.

We have completed the review of this application as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft physician labeling dated July 16, 1997. Accordingly, the application is approved effective on the date of this letter.

Exhibit E

The final printed labeling (FPL) must be identical to the July 16, 1997, draft labeling for the package insert (PI) and titration starter packs; the bottle and carton lablels must be identical to the drafts submitted on June 30, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-381. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Margaret Simoneau, R.Ph., Project Manager, at 301-443-3510.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Exhibit F

NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREFOR

RELATED PATENT APPLICATIONS

None.

TECHNICAL FIELD

This invention generally relates to compositions of nicotinic acid useful for treating hyperlipidemia and methods of treating hyperlipidemia employing such compositions. More particularly, the present invention employs a composition of nicotinic acid, derivatives and mixtures thereof, and a swelling agent to form a time release sustaining composition for nocturnal or evening dosing. Specifically, the present invention employs a composition of nicotinic acid and hydroxypropyl methylcellulose to treat hyperlipidemia in a once per day oral dosage form given during the evening hours.

BACKGROUND OF THE INVENTION

Nicotinic acid has been used for many years in the treatment of hyperlipidemia. This compound has long been known to exhibit the beneficial effects of reducing total cholesterol, low density lipoproteins or "LDL cholesterol", triglycerides and lipoprotein a (Lp(a)) in the human body, while increasing desirable high density lipoproteins or "HDL cholesterol".

Because of certain side effects however, nicotinic acid has normally been administered three times per day after meals. This dosing regimen is known to provide a very beneficial effect on blood lipids as discussed in Knopp et al; "Contrasting Effects of Unmodified and Time-Release Forms of Niacin on Lipoproteins in Hyperlipidemic Subjects: Clues to Mechanism of Action of Niacin"; Metabolism 34/7, 1985, page 647. The chief advantage of this profile is the ability of nicotinic acid to decrease total cholesterol, LDL cholesterol, triglycerides and Lp (a) while increasing HDL particles. While such a regimen does produce beneficial effects, cutaneous flushing and the like still often occurs in the hyperlipidemics to whom the compound is administered.

In order to avoid or reduce the undesirable side effects, a number of materials have been suggested for administration with an effective antihyperlipidemic amount of nicotinic acid, including guar gum in U.S. Pat. No. 4,965,252, and mineral salts as disclosed in U.S. Pat. No. 5,023,245; or inorganic magnesium salts as reported in U.S.

Pat. No. 4,911,917. These materials have been shown to reduce various of the side effects commonly associated with nicotinic acid treatment.

Another method of avoiding or reducing the side effects associated with immediate release niacin is the use of sustained release formulations. Sustained release formulations are designed to slowly release the compound from the tablet or capsule. The slow drug release reduces and prolongs blood levels of drug and thus minimizes the side effects. Sustained release formulations of niacin have been developed, such as Nicobid™ capsules (Rhone-Poulenc Rorer), Endur-acin™ (Innovite Corporation) and Pat. No. 5,126,145 which describes a sustained release niacin formulation containing two different types of hydroxypropyl methylcellulose and a hydrophobic component.

Studies in hyperlipidemic patients have been conducted with a number of sustained release niacin products. These studies have demonstrated that the sustained release products do not have the same advantageous lipid altering effects as immediate release niacin, and in fact often have a worse side effect profile compared to the immediate release product. The major disadvantage of the sustained release formulations, as can be seen in Knopp et al., 1985, is the significantly lower reduction in triglycerides (-2% for the sustained release versus -38% for the immediate release) and lower increase in HDL cholesterol, represented as HDL_2 particles which are known by the art to be most beneficial, (-5% for the sustained release versus +37% for the immediate release).

Additionally, sustained release niacin formulations have been noted as causing greater incidences of liver toxicity as described in Henken et al (Am J Med 91:1991 1991) and Dalton et al (Am J Med 93: 102 1992). There is also great concern regarding the potential of these formulations in disrupting glucose metabolism and uric acid levels.

Therefore, it can be seen from the scientific literature that there is a need for development of a sustained release niacin formulation and a method of delivering said formulation which would provide hyperlipidemic patients with "balanced lipid alteration", i.e. reductions in total cholesterol, LDL cholesterol, triglycerides and Lp(a) as well as increases in HDL particles, with an acceptable safety profile, especially as regards liver toxicity and effects on glucose metabolism and uric acid levels.

It is known that in the human body, much of the body's cholesterol is synthesized during the evening and especially during periodic physiological loss of consciousness or "sleep". While the above discussed nicotinic acid compositions exhibit an ability to reduce total cholesterol, LDL cholesterol, triglycerides and Lp(a),

as well as raising HDL cholesterol levels, they are all normally administered two-three times per day after meals. Hence, when the body's cholesterol and triglyceride synthesis mechanisms are at peak performance, nicotinic acid levels are at their lowest.

A need exists therefore, for a substained release formulation of nicotinic acid, and a method for the administration thereof, which can be administered once per day and which will substantially ensure that most of the nicotinic acid is released to the body during times of peak cholesterol synthesis while not producing any adverse effects on the liver, glucose metabolism or uric acid levels.

SUMMARY OF THE INVENTION

It is therefore, an object of the present invention to provide a composition of nicotinic acid or any compound which is metabolized by the body to form nicotinic acid for treating hyperlipidemia.

It is another object of the present invention to provide a composition as above, which has a time release sustaining characteristic.

It is yet another object of the present invention to provide a method for employing a composition as above, for treating hyperlipidemia.

At least one or more of the foregoing objects, together with the advantages thereof over the known art relating to the treatment of hyperlipidemia, which shall become apparent from the specification which follows, are accomplished by the invention as hereinafter described and claimed.

In general the present invention provides an improved antihyperlipidemia composition of the oral type employing an effective antihyperlipidemic amount of nicotinic acid, wherein the improvement comprises compounding the nicotinic acid with from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose per hundred parts by weight of tablet or formulation.

The present invention also provides an orally administered antihyperlipidemia composition which comprises from about 30% to about 90% parts by weight of nicotinic acid; and, from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose.

The present invention also includes a method of treating hyperlipidemia in a hyperlipidemic having a substantially periodic physiological loss of consciousness. The method comprises the steps of forming a composition which comprises an effective antihyperlipidemic amount of nicotinic acid and an amount of excipients to provide sustained release of drug. The method also includes the step of orally

administering the composition to the hyperlipidemic prior to each periodic physiological loss of consciousness.

PREFERRED EMBODIMENTS FOR CARRYING OUT THE INVENTION

The present invention employs nicotinic acid or a compound other than nicotinic acid itself which the body metabolizes into nicotinic acid, thus producing the same effect as described herein. The other compounds specifically include, but are not limited to the following: nicotinyl alcohol tartrate, d-glucitol hexanicotinate, aluminum nicotinate, niceritrol and d,l-alpha-tocopheryl nicotinate. Each such compound will be collectively referred to hereinbelow by "nicotinic acid."

As stated hereinabove, nicotinic acid has been employed in the past for the treatment of hyperlipidemia, which condition is characterized by the presence of excess fats such as cholesterols and triglycerides, in the blood stream. According to the present invention, a sustained release composition of nicotinic acid is prepared as an example. By "sustained release" it is understood to mean a composition which when orally administered to a patient to be treated, the active ingredient will be released for absorption into the blood stream over a period of time. For example, it is preferred that in a dosage of about 1500 milligrams (hereinafter "mgs") of nicotinic acid, approximately 100 percent of the nicotinic acid will be released to the blood stream in about 6 to about 24 hours.

The specific sustained release composition according to the present invention employs an effective antihyperlipidemic amount of nicotinic acid. By "effective antihyperlipidemic amount" it is understood to mean an amount which when orally administered to a patient to be treated, will have a beneficial effect upon the physiology of the patient, to include at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream. An exemplary effective antihyperlipidemic amount of nicotinic acid would be from about 250 mgs to about 3000 mgs of nicotinic acid to be administered according to the invention as will be more fully described hereinbelow. This amount will vary dependent upon a number of variables, including the physiological needs of the patient to be treated.

Preferably, there is also included in the sustained release composition according to the present invention, a swelling agent which is compounded with the nicotinic acid, such that when the composition is orally administered to the patient, the swelling agent will swell over time in the patient's gastrointestinal tract, and release the active

nicotinic acid, or a compound which produces nicotinic acid into the gastrointestinal system for absorption into the blood stream, over a period of time. As is known in the art, such swelling agents and amounts thereof, may be preselected in order to control the time release of the active ingredient. Such swelling agents include, but are not limited to, polymers such as sodium carboxymethylcellulose and ethylcellulose and waxes such as bees wax and natural materials such as gums and gelatins or mixtures of any of the above. Because the amount of the swelling agent will vary depending upon the nature of the agent, the time release needs of the patient and the like, it is preferred to employ amounts of the agent which will accomplish the objects of the invention.

An exemplary and preferred swelling agent is hydroxypropyl methylcellulose, in an amount ranging from about 5% to about 50% parts by weight per 100 parts by weight of tablet or formulation. The preferred example will ensure a sustained time release over a period of approximately 6-24 hours as demonstrated by in vitro dissolution techniques known to the art.

A binder may also be employed in the present compositions. While any known binding material is useful in the present invention, it is preferred to employ a material such as one or more of a group of polymers having the repeating unit of 1-ethenyl-2-pyrrolidinone. These polymers generally have molecular weights of between about 10,000 and 700,000, and are also known as "povidone".

Amounts of the binder material will of course, vary depending upon the nature of the binder and the amount of other ingredients of the composition. An exemplary amount of povidone in the present compositions would be from about 1% to about 5% by weight of povidone per 100 parts by weight of the total formulation.

Processing aids such as lubricants, including stearic acid, may also be employed, as is known in the art. An exemplary amount of stearic acid in the present compositions would be from about 0.5% to about 2.0% by weight per 100 parts by weight of tablet or formulation.

As was discussed hereinabove, it is known that much of the lipids in the human body are produced therein during the evening hours and especially during episodes of periodic physiological loss of consciousness or "sleep". By "periodic" it is understood to mean in a substantially uniform repeating pattern. For example, an adult may sleep approximately 8 hours per day. By being administered prior to each periodic physiological loss of consciousness, that is, orally administering the composition during the evening after dinner or as the person lies down to go to sleep, the present composition is capable of providing effective antihyperlipidemic amounts of nicotinic

acid to the body during times of peak lipid production or synthesis.

Furthermore, because the composition is orally administered prior to sleep, larger amounts of the active ingredient nicotinic acid is available during lipid synthesis times than if the composition is administered during hours when the patient is awake, i.e., in the morning or afternoon hours. Hence, less nicotinic acid may be required to be administered than would otherwise be required with compositions heretofore known in the art, while achieving substantially similar or even superior antihyperlipidemia results for at least one or more of the lipoproteins or particles discussed above. Because less nicotinic acid is administered and because the invention specifically describes once a day dosing, there is a lesser amount of the side effects as discussed hereinabove. The time release sustaining compositions according to the present invention ensure that effective antihyperlipidemia amounts of nicotinic acid are released to the patient during times of lipid production.

General Experimental

In order to demonstrate the effectiveness of the compositions and method of the present invention over known antihyperlipidemia compositions and methods heretofore known in the art, a number of substantially identical composition were prepared according to the disclosure hereinabove. The composition ingredients and amounts are listed in TABLE I hereinbelow.

TABLE I
Test Tablet Composition

Ingredient	375 mg	500 mg	750 mg
Nicotinic Acid	375.0	500.0	750.0
Hyroxypropyl methylcellulose	188.7	203.0	204.7
Povidone	12.9	17.2	25.9
Stearic Acid	5.8	7.3	9.9
TOTAL	582.4 mg	727.5 mg	990.5 mg

The ingredients were compounded together to form a tablet. Two study groups consisting of eleven and fourteen patients each were formed. Blood samples were taken from the patients, and tested for total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol to establish baseline levels from which fluctuations in these lipids could be compared. The patients were then placed upon a regimen of the above discussed tablets, totaling approximately 1500 mg of nicotinic acid, once per day before going to bed. After eight weeks of this regimen, the patients were again tested for lipid profiles. The results of the tests conducted at eight weeks, showing the changes in the lipid profiles as a percentage change from the baseline, are reported in the table hereinbelow. Positive numbers reflect percentage increases and negative numbers reflect percentage decreases in this table.

TABLE II

Patient Study Lipid Profile Data

	Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL_2-C	Lp(a)
	GROUP A							
	1	-8.2	-12.0	NA	-17.3	22.0	NA	NA
	2	-5.9	-27.0	NA	-28.7	65.0	NA	NA
	3	-15.1	-13.0	NA	-22.0	-9.1	NA	NA
	4	-3.3	-10.0	NA	61.6	3.8	NA	NA
	5	-16.5	-17.7	NA	-28.8	11.1	NA	NA
	6	-12.4	-25.9	NA	-42.0	51.6	NA	NA
	7	-24.2	-31.4	NA	-39.4	12.5	NA	NA
	8	-6.7	-7.4	NA	-42.4	18.8	NA	NA
	9	4.5	1.1	NA	7.2	9.2	NA	NA
	10	2.8	-0.2	NA	-2.7	22.9	NA	NA
	11	-13.0	-9.4	NA	-54.0	44.3	NA	NA
	Mean	-8.9	-13.9	NA	-18.9	23.0	NA	NA
	p-Value	0.0004	0.0001		0.0371	0.0068		
	GROUP B							
	1	-19.2	-27.1	-24.4	-33.4	20.0	22.3	-81.9
	2	-32.2	-35.7	-28.0	-60.4	4.3	3.2	-25.3
	3	-21.4	-33.6	-35.6	-33.4	30.4	38.6	-17.4
	4	-19.9	-24.6	-15.1	-20.8	9.6	16.1	-27.0
	5	-3.3	-2.1	-29.4	-41.1	5.8	2.4	-22.4
	6	PATIENT WITHDREW FROM STUDY						
	7	23.1	-32.6	-42.6	-58.6	49.2	68.9	-14.3
	8	24.8	34.0	-28.4	5.5	6.5	-6.8	NA
	9	10.1	12.0	-16.8	-11.6	20.7	-12.3	40.6
	10	-2.9	-7.7	-28.0	-59.0	53.1	70.5	-41.2
	11	-10.5	-18.8	-25.3	-53.4	31.8	39.7	NA
	12	-20.0	-30.8	-30.4	11.7	21.1	25.0	-28.4
	13	17.4	16.8	-17.5	-17.5	51.3	51.9	38.5
	14	-9.4	-16.6	-32.0	-46.9	52.3	67.6	17.6

TABLE II Continued

Mean	-8.7	-12.8	-32.2	-27.2	25.3	30.1	-17.9
p-Value	0.0002	<0.0001	0.0001	<0.001	<0.0001	0.0002	<0.0188
Combined	-8.7	-13.3	Gp B	-26.1	25.3	Gp B	Gp B
p-Value	0.0002	<0.0001	only	<.0001	<0.0001	only	only

The data reported in TABLE II shows that the LDL levels in the Group A patients had a mean decrease of -13.9% and triglyceride decrease of -18.9%. HDL cholesterol levels, the beneficial cholesterol, were raised by 23.0% in this Group. Similar results were obtained with the Group B patients. These studies demonstrate that dosing the sustained release formulation during the evening hours or at night provides reductions in LDL cholesterol levels equal to immediate release niacin on a milligram per milligram basis, but superior reductions in triglyceride reductions when compared to sustained release formulations dosed during daytime hours on a milligram per milligram basis. Additionally, the increases in HDL cholesterol obtained from dosing the sustained release formulation during the evening or at night were +23.0% for one group and +25.3% for the other group. Dosing during the evening therefore provides reduction in LDL cholesterol plus significant decreases in triglycerides and increases in HDL cholesterol with once-a-day dosing.

Groups A and B were also tested for liver enzymes (AST, ALT and Alkaline Phosphatase), uric acid and fasting glucose levels at the start of the study described hereinabove (to form a baseline) and at two, four and eight week intervals. The results of these tests are listed in TABLES III-VII hereinbelow.

TABLE III

THE EFFECT OF NIASPAN™ THERAPY ON AST (SGOT) LEVELS (U/L)

(1500 mgs dosed once-a-day at night)

(n = 28)

		Weeks Of Therapy With NIASPAN™				
Pt #		Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A						
	1	28	29	25	24	0-50
	2	24	25	24	26	0-50
	3	17	18	22	21	0-50
	4	14	16	15	17	0-50
	5	22	NA	32	52	0-50
	6	21	17	17	14	0-50
	7	17	17	14	18	0-50
	8	20	21	22	22	0-50
	9	16	16	17	20	0-50
	10	18	21	21	25	0-50
	11	21	21	22	21	0-50
GROUP B						
	1	23	25	38	33	0-50
	2	20	20	21	21	0-50
	3	15	20	18	19	0-50
	4	25	22	25	26	0-50
	5	23	21	17	18	0-50
	6	PATIENT WITHDREW DUE TO FLUSHING				
	7	21	18	18	19	0-50
	8	18	19	18	19	0-50
	9	15	16	18	15	0-50
	10	16	15	19	28	0-50
	11	20	22	24	28	0-50
	12	23	25	28	22	0-50
	13	20	15	20	19	0-50

TABLE III Continued

	14	18	25	20	18	0-50
5	Combined Mean	19.8	20.4	20.8	21.1	
	Change From Baseline		+3.0%	+5.1%	+6.6%	

10

Level of Significance: p=0.4141

TABLE IV

THE EFFECT OF NIASPAN™ THERAPY ON ALT (SGPT) LEVELS (U/L)

(1500 mgs dosed once-a-day at night)

(n = 28)

	Pt #	Baseline	Weeks Of Therapy With NIASPAN™ 2 Wks.	4 Wks.	8 Wks.	Reference Range
	GROUP A					
	1	32	28	39	30	0-55
	2	24	25	23	26	0-55
	3	18	23	30	30	0-55
	4	7	13	14	14	0-55
	5	14	NA	43	46	0-55
	6	22	11	14	10	0-55
	7	9	7	11	7	0-55
	8	16	18	23	21	0-55
	9	14	17	20	14	0-55
	10	14	15	17	19	0-55
	11	18	18	20	16	0-55
	GROUP B					
	1	16	17	27	29	0-55
	2	16	14	15	22	0-55
	3	13	21	13	16	0-55
	4	23	20	26	17	0-55
	5	21	23	17	15	0-55
	6	PATIENT WITHDREW DUE TO FLUSHING				
	7	21	16	18	21	0-55
	8	18	20	17	18	0-55
	9	11	5	11	8	0-55
	10	8	10	14	17	0-55
	11	17	12	18	16	0-55
	12	14	18	20	16	0-55
	13	14	NA	11	10	0-55

TABLE IV Continued

	14	23	23	19	19	0-55
5	Combined Mean	17.7	17.5	19.3	18.2	
	Change From Baseline		-1.1%	9.0%	+2.8%	

10 Level of Significance: p=0.3424

TABLE V

THE EFFECT OF NIASPAN™ THERAPY ON ALKALINE PHOSPHATASE LEVELS (U/L)

(1500 mgs dosed once-a-day at night)
(n = 28)

	Pt #	Baseline	Weeks Of Therapy With NIASPAN™ 2 Wks.	4 Wks.	8 Wks.	Reference Range
	GROUP A					
	1	52	56	57	55	20-140
	2	103	100	89	102	20-140
	3	54	45	53	51	20-140
	4	70	68	71	91	20-140
	5	77	NA	74	81	20-140
	6	55	48	49	51	20-140
	7	72	71	79	75	20-140
	8	55	49	47	50	20-140
	9	53	55	56	45	20-140
	10	74	73	75	75	20-140
	11	18	18	20	16	20-140
	GROUP B					
	1	73	67	89	95	20-140
	2	82	64	72	71	20-140
	3	73	69	72	82	20-140
	4	37	36	37	38	20-140
	5	65	53	54	61	20-140
	6	PATIENT WITHDREW DUE TO FLUSHING				
	7	64	58	58	58	20-140
	8	79	78	65	73	20-140
	9	94	92	103	93	20-140
	10	69	67	70	65	20-140
	11	59	67	63	72	20-140
	12	65	59	59	63	20-140
	13	64	68	66	64	20-140

TABLE V Continued

	14	72	61	59	64	20-140
5	Combined Mean	65.5	61.5	63.3	65.8	
	Change From Baseline		-6.1%	-3.4%	+0.005%	

10 Level of Significance: p=0.0236

TABLE VI

THE EFFECT OF NIASPAN™ THERAPY ON URIC ACID LEVELS (mg/dL)

(1500 mgs dosed once-a-day at night)
(n = 28)

	Weeks Of Therapy With NIASPAN™				
Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	5.2	5.0	4.8	4.3	4.0-8.5
2	4.0	4.6	4.5	6.2	2.5-7.5
3	6.3	7.0	6.5	6.2	4.0-8.5
4	3.1	4.6	4.2	3.8	2.5-7.5
5	3.4	NA	3.3	4.2	2.5-7.5
6	6.6	5.5	5.6	4.7	4.0-8.5
7	3.8	4.5	4.3	4.9	2.5-7.5
8	4.4	3.8	5.1	4.5	2.5-7.5
9	3.9	4.5	4.6	3.5	2.5-7.5
10	2.6	2.9	2.8	2.7	2.5-7.5
11	4.7	5.5	5.2	5.3	2.5-7.5
GROUP B					
1	3.7	4.2	4.7	3.5	2.5-7.5
2	2.8	3.5	3.6	2.3	4.0-8.5
3	4.2	5.3	5.5	5.3	2.5-7.5
4	4.7	3.9	5.1	3.6	4.0-8.5
5	3.7	4.1	4.1	3.8	2.5-7.5
6	PATIENT WITHDREW DUE TO FLUSHING				
7	5.8	6.6	6.6	6.8	2.5-7.5
8	4.7	4.3	5.4	5.6	2.5-7.5
9	3.7	4.6	5.1	3.8	2.5-7.5
10	4.2	5.0	4.4	8.5	2.5-7.5
11	1.9	3.0	2.8	5.0	2.5-7.5
12	5.6	5.4	6.2	5.6	4.0-8.5
13	4.2	4.6	4.6	5.3	2.5-7.5

TABLE VI Continued

	14	5.5	5.4	6.1	5.3	2.5-7.5
5	Combined Mean	4.54	4.82	4.92	4.86	*p=0.3450
	Change From Baseline		+6.2%	+8.4%	+7.0%	

10 *Level of Significance: p=0.3450

TABLE VII

THE EFFECT OF NIASPAN™ THERAPY ON FASTING GLUCOSE LEVELS (mg/dL)

(1500 mgs dosed once-a-day at night)
(n = 28)

Pt #	Baseline	Weeks Of Therapy With NIASPAN™ 2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	114	122	123	110	70-115
2	101	105	107	101	80-125
3	99	98	109	103	70-115
4	100	118	94	94	80-125
5	89	NA	82	103	80-125
6	97	103	94	107	70-115
7	85	107	100	94	80-125
8	98	107	103	101	80-125
9	97	97	100	110	80-125
10	94	101	111	97	70-115
11	102	103	95	95	80-125
GROUP B					
1	101	97	83	99	70-115
2	90	95	96	89	80-125
3	96	98	95	97	70-115
4	116	139	113	125	80-125
5	88	92	91	95	70-115
6	PATIENT WITHDREW DUE TO FLUSHING				
7	106	114	118	117	70-115
8	95	106	106	108	70-115
9	81	92	84	92	70-115
10	108	117	122	105	70-115
11	85	106	106	108	70-115
12	92	89	101	86	80-125

TABLE VII Continued

13	99	105	94	100	70-125
14	100	108	84	107	70-125
Combined Mean	98.4	105.8	101.6	102.3	
Change From Baseline		+7.5%	+3.3%	+4.0%	

Level of Significance: p=0.0021

These results indicate that this sustained release dosage form caused no elevation in liver function tests (i.e., no liver damage), no elevations in uric acid and only a small, 7.5% increase in fasting glucose levels which in fact decreased during continued therapy.

Thus it should be evident that the compositions and method of the present invention are highly effective in controlling hyperlipidemia in hyperlipidemics, by reducing the levels of LDL cholesterol, triglyceride and Lp(a) while increasing HDL cholesterol levels. The present invention is also demonstrated not to cause elevations in liver function tests, uric acid or glucose levels for the hyperlipidemics.

Based upon the foregoing disclosure, it should now be apparent that the use of the compositions and methods described herein will carry out the objects set forth hereinabove. It is, therefore, to be understood that any variations evident fall within the scope of the claimed invention and thus, the selection of specific component elements can be determined without departing from the spirit of the invention herein disclosed and described. In particular, sustained release excipients, binders and processing aids according to the present invention are not necessarily limited to those exemplified hereinabove. Thus, the scope of the invention shall include all modifications and variations that my fall within the scope of the attached claims.

What is claimed is:

1. An antihyperlipidemic composition of the oral type employing an effective antihyperlipidemic amount of nicotinic acid or compound metabolized to nicotinic acid by the body, given once per day in the evening or at night to produce a significant reduction in total and LDL cholesterol as well as a significant reduction in triglycerides and Lp(a), with a significant increase in HDL cholesterol.

2. A composition, as set forth in Claim 1, comprising from about 250 parts to about 3000 parts by weight of nicotinic acid.

3. An antihyperlipidemic composition as set forth in Claim 1 which cause little or no serious liver damage, uric acid increases or elevations in fasting glucose levels.

4. An antihyperlipidemic composition as set forth in Claim 1 which has a release rate of nicotinic acid or compound metabolized by the body to nicotinic acid from about 2.0% per hour to about 25% per hour.

5. An antihyperlipidemic composition as set forth in Claim 1 which is comprised by formulating the active compound with from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose per 100 parts by weight of tablet or sustained release excipients.

6. A composition, as set forth in Claim 1, wherein the sustained release formulation or tablet contains from about 1 to about 4 parts by weight of binder per 100 parts by weight of tablet or sustained release formulation.

7. A composition, as set forth in Claim 4, wherein said binder is selected from the group consisting of polymers having the repeating unit 1-ethenyl-2-pyrrolidone.

8. A composition, as set forth in Claim 1, further comprising from about 0.5 to about 2.5 parts by weight of a lubricating agent per 100 parts by weight of tablet or sustained release formulation.

9. A composition, as set forth in Claim 6, wherein said lubricating agent is selected from the group consisting of stearic acid and magnesium stearate.

10. A composition, as set forth in Claim 1, wherein the nicotinic acid component has been substituted with a compound which is metabolized by the human body to form nicotinic acid.

11. A composition, as set forth in Claim 9, wherein the compound substituted for nicotinic acid is nicotinyl alcohol tartrate.

12. A composition, as set forth in Claim 10, wherein the amount of nicotinyl alcohol tartrate is from about 100 milligrams to about 500 milligrams per dosage unit.

13. A composition, as set forth in Claim 10, wherein the compound substituted for nicotinic acid is selected from the group: d-glucitol hexanicotinate, aluminum nicotinate, niceritrol and d, l-alpha-tocopheryl nicotinate.

14. A method for treating hyperlipidemia comprising dosing a sustained release form of niacin once per day in the evening or at night to provide a reduction in total and LDL cholesterol as well as a reduction in triglycerides and Lp(a), with a significant increase in HDL cholesterol, with substantially no liver enzyme toxicity.

ABSTRACT OF THE DISCLOSURE

An orally administered antihyperlipidemia composition according to the present invention includes from about 250 to about 3000 parts by weight of nicotinic acid, and from about 5 to about 50 parts by weight of hydroxypropyl methylcellulose. Also, a method of treating hyperlipidemia in a hyperlipidemic having a substantially periodic physiological loss of consciousness, includes the steps of forming a composition having an effective antihyperlipidemic amount of nicotinic acid and a time release sustaining amount of a swelling agent. The method also includes the step of orally administering the composition to the hyperlipidemic substantially immediately prior to each periodic physiological loss of consciousness.

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EDUCATION

Bachelor of Science, Chemistry, ACS Accredited
Ursinus College, Collegeville, Pennsylvania, 1988

RELEVANT EXPERIENCE

Kos Pharmaceuticals, Inc. October, 1990 – Present

Associate Director, Quality Control

Directed the Quality Control operations for Kos Pharmaceuticals, Inc. The department consisted of two department supervisors and eight analysts. Responsibilities included coordinating department activities in-line with production, stability and development/validation needs, establishing and implementing training programs and developing and administrating department budgets. Ensured department compliance with regulatory commitments and cGMPs.

Manager, Quality Control

Managed the day-to-day operations of the Quality Control and Analytical Development Laboratory. Ensured that work output was maintained and all work was conducted in conformance to cGMP guidelines. Provided testing and documentation support for the Niaspan® project

Senior Quality Control Analyst

Initially setup the Quality Control Laboratory for Kos Pharmaceuticals, Inc. Provided testing support utilizing HPLC, GC and wet chemical methods for drug assays, additives and packaging components in support of the Niaspan® project. Developed and validated analytical methods for characterizing of new pharmaceutical products under development.

Materials Processing Technology, Inc. September, 1989 - October, 1990

Senior Quality Control Analyst

Developed and validated analytical methods utilizing HPLC, GC and wet chemical methods for the Niaspan® project. Utilized developed methods for characterizing and testing drug actives, additives and packaging components in support of the Niaspan® project.

Eon Laboratories, Inc. (formerly Vitarine Pharmaceuticals, Inc) June, 1988 – September 1989

Quality Control Analyst

Quality Control testing on raw materials, intermediates and finished products Testing included dissolution, UV/Vis Spectrometry, Karl Fischer, HPLC, GC and IR. Conducted investigations of out of specification results. Reviewed notebooks and prepared regular status reports concerning relevant projects. Trained other analysts in the use of equipment and applicable project procedures.

Quality Control Technician

Routine Quality Control testing of raw materials, intermediates and finished products.